Venous thrombosis is not increased in younger women on genuine oestrogen postmenopausal hormonal replacement therapy: Results from the Danish Osteoporosis Prevention Study (DOPS)

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Dear Sir,

Until 1996, an underestimation of the risk of venous thrombosis (VT) during hormonal replacement therapy (HRT) may have resulted from too small studies, but then some case-control studies (1–5) and two large prospective studies, i.e. the “HERS” (6) and “Women Health Initiative” studies (7), clearly indicated a 2–4-fold increased risk of VT compared with non-users. However, the estrogen-alone arm of the Women Health Initiative study showed an only minor non-significantly increased risk of VT (8), and a case-control study examining HRT containing estradiol showed no overall increased risk, although it was increased during the first year of use (9). We have examined the frequency of VT in the Danish Osteoporosis Prevention Study (DOPS) where women were allocated to HRT or no treatment for ten years (10).

The study design of DOPS is described in detail by Mosekilde et al. (10). DOPS is a multicentre study of risk factors for osteoporosis, comprising 2,016 healthy postmenopausal women with a randomized arm [HRT (n=502); no treatment (n=504)], and a non-randomized arm in which the women chose themselves whether they wished treatment or not [HRT (n=221); no treatment (n=789)]. Eligible for inclusion were 45- to 58-year-old women with last menstrual bleeding within 3–24 months or menstrual irregularities with an elevated serum follicle-stimulating hormone (S-FSH), or hysterectomized women aged 45 to 52 years and elevated S-FSH. Exclusion criteria included metabolic bone disease, estrogen use within the past three months, malignancy, previous venous thrombosis, treatment at any time for > 6 months with glucocorticoids, and newly diagnosed or uncontrolled chronic disease (10). The mean ages at inclusion in the four groups “HRT, randomized”; “no HRT, randomized”; “HRT, non-randomized”; “no HRT, non-randomized” were 50.0, 50.4, 50.5, and 51.2 years, respectively. The fractions of hysterectomized women in the same four groups were 19.0%, 19.2%, 18.3%, and 11.1%, respectively. Current smokers at inclusion were: 43%, 45%, 46%, and 37%, respectively, and the mean of BMI was 25.3, 25.2, 23.9, and 25.3 kg/m², respectively, in the four groups (10).

References


The study was conducted in accordance with the Helsinki II declaration, approved by the local Ethics Committees, and all participants gave informed consent.

Non-hysterectomized women were treated with sequential therapy, oestradiol 2 mg, days 1–21, 1 mg days 22–28 and norethisteron acetate 1 mg, days 11–21 (Trisekvens®, NovoNordisk, Copenhagen, Denmark). Hysterectomized women received continuous treatment with 2 mg oestradiol (Estrofem®, NovoNordisk, Copenhagen, Denmark). Controls received no placebo. The table shows the flow of participants from invitation to the last control after 10 years where the study comprised 1,694 participants (see Table 1), i.e. 322 participants left the study during the 10 years because they wanted to discontinue, did not attend a control visit or died. The participants were controlled at baseline and after 1, 2, 3, 5 and 10 years. At each visit the participants were asked, among other things, about illnesses and any serious adverse events by a medical doctor using a structured questionnaire, and any concurrent illness was validated through files from hospitals etc. If a woman changed from treatment to no treatment or vice versa this was noted in her file but she continued to come to the visits. For participants who died during the study, death certificates were collected, and information on the cause of death was checked.

Table 1: Flow of the participants from invitation to participate through inclusion in the study and to 10 years follow-up. The numbers in the parentheses are the fraction of the women in each group calculated as percentage of the women included at start in the same group.

| Invited: 47,720 | Responded: 23,500 |
| Met inclusion criteria: ~3,500 |
| Included: 2,016 |

<table>
<thead>
<tr>
<th></th>
<th>HRT</th>
<th>non-HRT</th>
<th>HRT</th>
<th>non-HRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Included</td>
<td>502</td>
<td>504</td>
<td>221</td>
<td>789</td>
</tr>
<tr>
<td>Left study</td>
<td>75 (14.9%)</td>
<td>90 (17.9%)</td>
<td>26 (11.8%)</td>
<td>131 (16.6%)</td>
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<tr>
<td>After 10 years</td>
<td>427 (85.1%)</td>
<td>414 (82.1%)</td>
<td>195 (88.2%)</td>
<td>658 (83.4%)</td>
</tr>
<tr>
<td>Compliant</td>
<td>228 (45.4%)</td>
<td>299 (59.3%)</td>
<td>107 (48.4%)</td>
<td>573 (72.6%)</td>
</tr>
<tr>
<td>Shift HRT to non-HRT</td>
<td>non-HRT: 199 (39.6%)</td>
<td>HRT: 115 (22.8%)</td>
<td>non-HRT: 88 (39.8%)</td>
<td>HRT: 85 (10.8%)</td>
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</table>

Only three cases of VT, two deep venous thromboses (confirmed by phlebography or ultrasound) and one pulmonary embolism (mismatch between pulmonary ventilation-perfusion scintigrams) were registered, and all the events occurred in women from the non-HRT-group, one randomized subject and two by individual choice. One DVT occurred postoperatively in a non-smoker whereas the two other events occurred spontaneously in heavy smokers.

In the non-HRT-group (“intention-to-treat”) the event-rate was 2.5*10⁻⁴ women-years, and 0 in the HRT-group. This was not statistically different (p=0.29), but the results exclude a four times increased risk of VT using HRT (p=0.036), whereas a two or three times increased risk cannot be excluded (p= 0.14 and p= 0.07, respectively).

Fifty-three (7.4%) of the women allocated to HRT were heterozygous for factor V Leiden, and one woman was homozygous. Thus, we registered about 5,000 women-years without VT during HRT and more than 400 women-years without VT during HRT in women positive for factor V Leiden.

Albeit small, our study showed no increased risk of VT in younger postmenopausal women on HRT. We actually found a lower risk of VT during HRT, but this was not statistically significant, and the results cannot exclude a minor increase of the risk. Although all participants were thoroughly interviewed at each control, we cannot exclude the possibility that documentation was not complete, but it is unlikely. The frequency of VT is also comparable to the studies conducted in 1996/97 (1, 2, 5), but much lower compared with HERS (6) and WHI (7) in which the participants were older and HRT contained equine oestrogen and a different progestogen, and, furthermore, the inclusion/exclusion criteria were different – e.g. in the present study women with previous VT were excluded. An obvious limitation of the study is the low incidence of VT which reduces the power, and another limitation is that the study was not designed for the purpose to investigate the frequency of VT. The strength of the study is the prospective design, and the data definitely exclude a high risk of VT during HRT. Although no firm conclusions can be made, the study may indicate that genuine oestrogen is less thrombogenic than equine oestrogen as also suggested earlier by Høibraaten et al. (9).

During the study period of ten years a considerable number of women changed from HRT to no treatment or vice versa (see Table 1), but the women with thromboses had not received HRT at any time, i.e. the conclusion is the same whether intention-to-treat or per-protocol analysis of data is used. In conclusion, our study indicates that the risk of VT is low for younger postmenopausal women receiving HRT.

References